Remarks

The Declaration

The declaration of inventorship has been revised to claim priority under 35 U.S.C. 120 and 365(c), as requested by the examiner. This is being sent under separate cover.

Amendments to the Claims

Claims 20-24 and 30-49 have been cancelled as drawn to non-elected inventions and will be pursued in divisional applications.

Claims 25-29 have been amended to depend from claim 1, and are therefore drawn to the same invention as claims 1-18, elected in response to the original restriction requirement.

Claim 1, and claims dependent thereon, have been amended to clarify the subject matter. It is apparent from the examiner's comments and from the undersigned's own review, that the previous language, while technically of the same scope, was confusing. If the proposed language is still believed to be confusing, please call the undersigned to work out some agreed upon language. The proposed language is an attempt to clarify primarily through the delineation of the essential technical features of the claimed method, rather than functional language. No new matter is added.

The Claimed Invention

The claimed invention is based on the discovery that one can kill cells which present on their surface a peptide derived from a molecule which is chacteristic of a particular disease - such as a protein that is overexpressed by the diseased cells, a protein derived from a pathogen or infectious agent, or a mutated or abnormal protein that is made by the diseased cells. The claim language has been clarified to note that this peptide is presented on the surface of these cells to

be killed as part of the HLA class I complex. (It is noted that this particular aspect of the method was previously argued but not in the claim language) It has also been clarified that the cells are killed by administering cytotoxic T lymphocytes which have two critical requirements: (1) they are of a different HLA class I type than the cells to be killed and (2) they specifically recognize the peptide which is presented on the surface of the cells to be killed. See, for example, page 11, lines 11-15; page 10, lines 7-8, and page 11, lines 5-15.

As discussed more fully below, it is the first point that most clearly distinguishes the prior art, since none of the prior art recognize the need to use killer cells which are of a different HLA class I type than the cells to be killed.

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 1-9 and 14-18 were rejected under 35 U.S.C. § 112, second paragraph, as indefinite. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The claims were objected to for the use of the phrase "diseased cells which cells contain or are associated with an abnormal molecule or abnormally elevated amount of a molecule". This language has been replaced so that the claim now reads:

1. (Twice amended) A method of killing cells in a patient with a disease characterized by expression by the patient of an abnormal molecule or an abnormally elevated amount of a molecule as compared to the non-diseased state, or by expression of an infectious agent protein, the method comprising

administering to the patient a therapeutically effective amount of cytotoxic T lymphocytes (CTL),

wherein the CTLs are of a different HLA class I (or equivalent) than the cells to be killed, and

the CTLs specifically recognize a peptide portion of the abnormal molecule or molecule which is abnormally elevated in patients with the disease or the infectious agent protein, when the peptide is presented by the HLA class I complex (or equivalent) on the surface of cells to be killed and kill the presenting cells.

It is believed that it is now clear that the disease state is characterized by a particular molecule (which is either overexpressed, abnormal compared to the non-diseased state, or a product of a pathogen or other infectious organism), and that a peptide portion of this molecule is bound by the HLA class I complex on the surface of the cells to be killed (it is also believed that the language regarding treating has been made more specific by denoting that the CTLs kill those cells presenting peptides derived from these molecules). The language "associated with" has been deleted.

Rejection Under 35 U.S.C. § 102

Claims 1-9, 14, 16 and 18 were rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 5,928,639 to Slavin et al. as evidenced by Wu et al., *J. Biol. Chem.* 270:5944 (1995). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Slavin specifically requires treating a disease such as cancer using ***allogeneic*** lymphocytes. See, for example, col. 3, lines 40-44, which recite "HLA-compatible, allogeneic peripheral blood lymphocytes". See also col. 5, lines 45-47, "The HLA-compatible allogeneic cells employed in the present invention preferably are fully HLA-matched with the patient."

As discussed above, the claimed method requires the cytotoxic T lymphocytes to have a different HLA class I type than the cells to be killed. Therefore, Slavin does not disclose the claimed method.

Wu, et al. teaches nothing with regard to selection of the HLA class I type.

Rejection Under 35 U.S.C. § 103

Claims 1-9 and 14-18 were rejected under 35 U.S.C. § 103(a) as obvious over Kohler et al., *Cancer Immunol. Immunother.* 26:74 (1988), or U.S. Patent No. 5,994,523 to Kawakami et al., in view of Yin et al., *Eur. J. Immunol.* 24:1990 (1988), Huang et al., *Cancer Immunol. Immunother.* 38:399 (1994), U.S. Patent No. 5,928,639 to Slavin et al., or Wu et al., *J. Biol. Chem.* 270:5944 (1995). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Kohler, et al., describes treating cancer patients with "alloactivated HLA haploidentical lymphocytes" (summary, page 74).

Kawakami, et al., discloses a peptide which is produced by melanoma cells, that can be used to target the melanoma cells, for diagnosis, prognosis, or as a vaccine. The section referred to by the examiner in the previous office action (col. 36, line 60) (none were specifically referenced in this office action) describes the use of radiolabelled TIL and chemotherapy (cylcophosphamide and IL-2) to kill melanomas. The TILs localized in the tumors; there is no indication they bound to the antigen and elicited cell death. Rather, cell death was caused by the chemotherapy, which was monitored by the radiolabeled TIL. TILs are discussed generally at col. 1, lines 38-67, and described specifically at col. 31, line 25, as HLA-A2 restricted melanoma specific CTL lines. As stated at col. 31, lines 27-59, these CTLs "recognized autologous and

most allogeneic fresh or cultured melanoma cells expressing HLA-A2, but did not recognize HLA-A2- melanomals or HLA-A2+ non-melanoma cell lines." There is no discussion relating to HLA class I molecules or type other than in passing at col. 1, lines 57-63.

Yin, et al., describes an unusual example where the "peptide presentation requires murine H-2 class I molecules but is not class I allele restricted" (abstract, page 1988). Not only is there no discussion about explicitly needing CTLs which are of a different HLA class I type, there is a teaching that at least in this one case, the reaction was not HLA class I type restricted (although there was MHC class II restriction).

Huang, et al. describes a series of experiments in which the reactivity of CTLs towards allogeneic melanoma cells was measured. The CTLs were specific for the melanoma cells; some were not HLA restricted. The findings are summarized in the abstract, leading to the conclusion "This reinforces clinical findings that allogeneic melanomas can substitute for autologous tumors".

In summary, the examiner is completely correct in noting that it was well known that CTL mediated lysis is typically considered to be antigen specific. What is new and now clearly defined by the claims, is the discovery that this reaction, previously thought to have to be used in combination with allogeneic cells, i.e., cells in which there is complete identity of the HLA class type I molecules, can instead occur, and to an even greater effect, when the CTLs are selected to have disparate HLA class type I molecules from the cells to be killed.

As demonstrated by the enclosed copy of Immunobiology, Janeway and Travers, 2nd edition, 1996, Figure 6.16, page 6.18, it is generally believed that T cells of an individual do not include cells capable of recognizing antigens in the context of foreign HLA molecules. CTL are

stimulated by allogeneic HLA molecules which they recognize directly (in a peptide non-specific fashion) or by up to 10,000 different peptide epitopes (derived from cellular proteins) that are normally present in the peptide binding groove of allogeneic HLA molecules. Hence allo-reactive CTL are polyspecific (direct HLA and 10,000 peptides) which limits the clinical usefulness of this response. In contrast, the claimed method makes the response specific for the peptide epitope in the absence of the common HLA class I type.

As a result, the CTLs can be directed against epitopes which are never reached in a compatible response (i.e., where the HLA molecule presenting the antigen is matched) because in that situation the immune system is tolerant. This method is particularly advantageous in relation to the treatment of diseases in which there is abnormal expression of a normal antigen because the T cell repertoire of HLA-mismatched donors is not tolerant to peptides presented by the patient's HLA molecules. Thus, it is possible to isolate CTL from HLA-mismatched donors which are specific for peptides derived from cellular proteins abnormally expressed in the patient's diseased cell. Because of tolerance, such CTLs cannot be isolated from the patient's own T cell repertoire, or from the repertoire of MHC-matched donors. The method may therefore be used for non-self antigens such as those that occur in infectious disease, as well as for self-antigens.

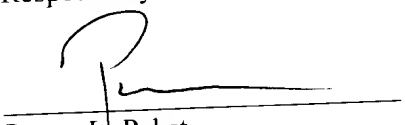
The enclosed papers Sadovnikova, et al., (1998) Eur. J. Immunol. 28, 193-200 and Gao, et al., (2000) Blood 95, 2198-2203, show that the claimed method works in humans. In the first paper, HLA-A2-negative donors were used to isolate tumor-reactive CTL specific for cyclin-D1 peptidds presented by HLA-A2 Class I molecules. In the second paper, HLA-A2-negative

donors were used to isolate tumor reactive CTL specific for WT-1 peptides presented by HLA-A2 Class I molecules.

The cited publications all fail to disclose or suggest, either alone or in combination, the use of CTL specific for a disease-associated antigens and the use of CTL from an individual who does not carry the HLA Class I molecule type which in the patient presents the disease antigen. In fact, the cited publications teach away from the use of such CTL. Accordingly, the claimed method is not obvious in view of the cited publications.

Allowance of claims 1-18 and 25-29 is earnestly solicited.

Respectfully submitted,



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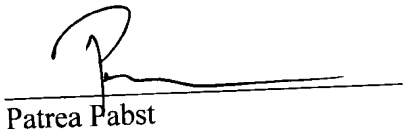

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Date: March 12, 2001

Appendix: Marked up Claims As Pending After Entry of the Amendment

1. (Twice amended) A method of [treating] killing cells in a patient with a disease characterized by [wherein the patient contains diseased cells which cells contain, or are associated with,] expression by the patient of an abnormal molecule or an abnormally elevated amount of a molecule as compared to the non-diseased state, or by expression of an infectious agent protein [and which cells are capable of presenting at least part of the molecule on their surface by a particular HLA class I (or equivalent) molecule], the method comprising

administering to the patient a therapeutically effective amount of cytotoxic T lymphocytes (CTL),

wherein the CTLs are of a different HLA class I (or equivalent) than the cells to be killed, and

the CTLs specifically recognize a peptide portion of the abnormal molecule or molecule which is abnormally elevated in patients with the disease or the infectious agent protein, when the peptide is presented by the HLA class I complex (or equivalent) on the surface of cells to be killed, and kill the presenting cells [which are selected to specifically recognize at least part of the molecule when presented by an HLA class I (or equivalent) molecule on the surface of a cell characterised in that the cytotoxic T lymphocytes are derived from an individual which individual does not carry the HLA class I (or equivalent) molecule type which, in the patient, presents at least part of the abnormal molecule contained in, or associated with, the diseased cells of the patient or presents an abnormally elevated of the molecule contained in, or associated with, the diseased cells of the patient].

2. A method according to Claim 1 wherein the CTL are a clonal population of CTL.

3. (Amended) A method according to Claim 1 wherein the CTL are substantially free of other cell types.

4. (Amended) A method according to Claim 1 wherein the molecule is a polypeptide.

5. (Twice amended) A method according to Claim 4 wherein the polypeptide is a mutant polypeptide associated with the diseased cells.

6. (Amended) A method according to Claim 4 wherein the polypeptide is present at a higher level in the diseased cells compared to non-diseased cells.

7. (Amended) A method according to Claim 1 wherein the disease is a cancer.

8. A method according to Claim 7 wherein the cancer is any one of breast cancer; bladder cancer; lung cancer; prostrate cancer; thyroid cancer; leukaemias and lymphomas such as CML, ALL, AML, PML; colon cancer; glioma; seminoma; liver cancer; pancreatic cancer; bladder cancer; renal cancer; cervical cancer; testicular cancer; head and neck cancer; ovarian cancer; neuroblastoma and melanoma.

9. (Amended) A method according to Claim 1 wherein the disease is caused by a chronic viral infection.

10. (amended) A method according to Claim 9 wherein the virus is [any one] <u>selected from the group consisting</u> of HIV, papilloma virus, Epstein-Barr virus, HTLV-1, hepatitis B virus, hepatitis C virus and herpes virus.

11. A method according to Claim 10 wherein the virus is HIV.

12. (Amended) A method according to Claim 1 wherein the disease is associated with an abnormally elevated amount of a hormone.

13. (Amended) A method according to Claim 1 wherein the disease is a bacterial disease caused by a chronic bacterial infection.

14. (Amended) A method according to Claim 1 further comprising the step of determining the HLA class I (or equivalent) molecule type of the patient prior to administration of the CTL.

15. (Amended) A method according to Claim 14 wherein the type is determined using DNA typing.

16. (Amended) A method according to Claim 1 wherein the patient is human.

17. (Amended) A method according to Claim 14 wherein the cytotoxic T lymphocyte is selected from a library of CTL clones, the library comprising a plurality of CTL clones derived from individuals with differing HLA class I (or equivalent) molecule type and each CTL clone recognises the diseased cells.

18. (Amended) A method according to Claim 17 wherein each CTL clone recognises at least part of the same molecule contained in or associated with the diseased cells.

Please cancel claims 20-24.

25. (Twice Amended) A method according to Claim [23] 1 wherein the [diseased cell] cells to be killed are selected from the group consisting of [is any one of] a cancer cell, a virus-infected cell, a bacterium infected cell and a cell expressing an abnormally elevated amount of a hormone.

26. (Twice Amended) A method according to Claim [20] 1 wherein the [healthy individual] patient is a human.

27. (Twice Amended) A method according to Claim [26] 1 wherein the [selected] molecule is [any one] selected from the group consisting of cyclin D1, cyclin E, mdm 2, EGF-R, erb-B2, erb-B3, FGF-R, insulin-like growth factor receptor, Met, myc, p53, BCL-2, [ie mutant Ras,] mutant p53, a polypeptide associated with the BCR/ABL translocation in CML and ALL, mutant CSF-1 receptor, mutant APC, mutant RET, mutant EGFR, a polypeptide associated with PML/RARA translocation in PML, a polypeptide associated with E2A-PBX1 translocation in pre B leukaemias and in childhood acute leukaemias, human papilloma virus proteins, Epstein-Barr virus proteins, HTLV-1 proteins, hepatitis B [or] virus proteins, hepatitis C virus proteins, herpes-like virus proteins and HIV encoded proteins.

28. (Twice Amended) A method according to Claim [20] 1 further comprising determining the HLA Class I (or equivalent) type of the healthy individual.

29. (Amended) A method according to Claim 28 wherein the HLA class I (or equivalent) type is determined by DNA analysis.